

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/23374 A1

(51) International Patent Classification⁷: C07D 401/10,
413/10, 209/08, 403/10, 401/14, 401/12, A61P 25/24

Science Park South, Third Avenue, Harlow, Essex CM19
5AW (GB).

(21) International Application Number: PCT/EP00/09442

(74) Agent: WATERS, David, Martin; Corporate Intellectual
Property, SmithKline Beecham, Two New Horizons Court,
Brentford, Middlesex TW8 9EP (GB).

(22) International Filing Date:
21 September 2000 (21.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9922831.4 25 September 1999 (25.09.1999) GB
0001936.4 27 January 2000 (27.01.2000) GB
0013873.5 7 June 2000 (07.06.2000) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; New
Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

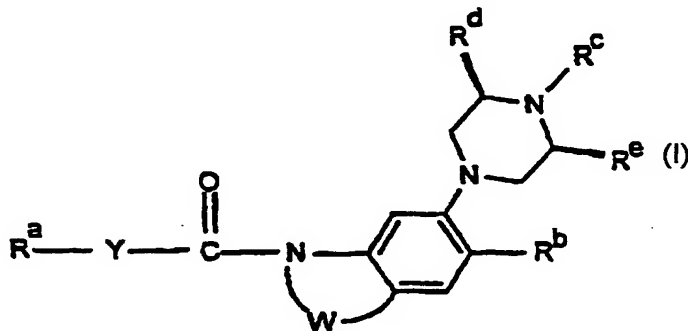
(75) Inventors/Applicants (*for US only*): MARSHALL,
Howard [GB/GB]; SmithKline Beecham Pharmaceuti-
cals, New Frontiers Science Park South, Third Avenue,
Harlow, Essex CM19 5AW (GB). THOMPSON, Mervyn
[GB/GB]; SmithKline Beecham Pharmaceuticals, New
Frontiers Science Park South, Third Avenue, Harlow, Es-
sex CM19 5AW (GB). WYMAN, Paul, Adrian [GB/GB];
SmithKline Beecham Pharmaceuticals, New Frontiers

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PIPERAZINE DERIVATIVES AS 5-HT_{1B} ANTAGONISTS



(57) Abstract: Piperazine derivatives of formula
(I) processes for their preparation, pharmaceutical
compositions containing them and to their use in
therapy as 5-HT_{1B} antagonists. W, Y, R^a-R^e are so defined
in the application.

WO 01/23374 A1

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WATERS, David, Martin
SmithKline Beecham
Corporate Intellectual Property
(CN9.25.1)
980 Great West Road
Brentford, Middlesex
TW8 9GS
ROYAUME-UNI

Date of mailing (day/month/year) 18 février 2002 (18.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference ADS/P32422	
International application No. PCT/EP00/09442	International filing date (day/month/year) 21 septembre 2000 (21.09.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address WATERS, David, Martin Corporate Intellectual Property SmithKline Beecham Two New Horizons Court Brentford Middlesex TW8 9EP United Kingdom	State of Nationality	State of Residence
	Telephone No. +44 127 964 4283	
	Facsimile No. +44 20 8975 6294	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address WATERS, David, Martin SmithKline Beecham Corporate Intellectual Property (CN9.25.1) 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom	State of Nationality	State of Residence
	Telephone No. +44 20 8047 5000	
	Facsimile No. +44 20 8047 6894	
	Teleprinter No.	

3. Further observations, if necessary:

The address of the chapter II agent has also been changed accordingly.

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Sangeeta JAIYA Telephone No.: (41-22) 338.83.38
---	--

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 12 July 2001 (12.07.01)	
International application No. PCT/EP00/09442	Applicant's or agent's file reference ADS/P32422
International filing date (day/month/year) 21 September 2000 (21.09.00)	Priority date (day/month/year) 25 September 1999 (25.09.99)
Applicant MARSHALL, Howard et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
20 April 2001 (20.04.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Charlotte ENGER Telephone No.: (41-22) 338.83.38
---	---

REC'D 08 OCT 2001

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference ADS/P32422	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/09442	International filing date (day/month/year) 21/09/2000	Priority date (day/month/year) 25/09/1999
International Patent Classification (IPC) or national classification and IPC C07D401/10		
Applicant SMITHKLINE BEECHAM P.L.C. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 20/04/2001	Date of completion of this report 04.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gettins, M Telephone No. +49 89 2399 8273



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09442

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-29 as originally filed

Claims, No.:

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09442

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5,9,10
	No:	Claims	1-4,6-8,11-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09442

- 1). Relevant prior art is provided by:
 - (A) EP533268
 - (B) WO9506637
 - (C) WO98/27058
 - (D) WO98/47885
 - (E) WO98/50358
 - (F) WO99/29666
- 2). The current application is novel vis-à-vis (A)-(F) primarily on account of the R^D and R^E alkyl substituents.
- 3). The current application seeks to solve the problem of making available further piperazine derivatives which can be used as 5-HT_{1B} antagonists. As indicated by the Applicant on page 1, older prior art documents which refer to 5-HT_{1D} activity would, in the light of the knowledge available at the filing date, would be considered to have a high chance of 5-HT_{1B} activity. The closest prior art is considered to be (D) or (E) (5-HT_{1B}) or (B) (5-HT_{1D} antagonists). The current application only differs from all said 3 said prior art documents in that the piperazine group is substituted by 2 alkyl groups. At least for the case where R^D and R^E are methyl this corresponds to the replacement of hydrogen by methyl. This would appear to be a minor change which would not be expected to lead to the qualitative loss of the desired activity. The change would not appear to be a major one in structural or electronic terms and optional substituents such those on P¹, P², P³ rings or R^C indicate that the desired activity can be expected to be retained when hydrogen is replaced by methyl. The solution proposed by the Applicant would appear to be an obvious one.

The Applicant was asked to demonstrate the presence of an inventive step for the current application e.g. by showing a quantitative superiority vis-à-vis the closest prior art. Test data submitted during the PCT phase shows that the R^d and R^e methyl substituents lead to an improved activity (improved selectivity for 5-HT_{1B} and improved antagonistic properties) vis-à-vis compounds where the corresponding substituent is hydrogen. Accordingly an inventive step can be acknowledged for the tested compounds. The question is how far can the inventive effect be generalised from the tested compounds to the current scope of

the claims. Since an inventive step has been shown for the novel feature a wide generalisation of the tested examples is possible. Additionally the other examples have also been considered. The generalisation is considered to be reasonable in so far as the claimed compounds can be considered to be homologues or analogues of the actual examples.

It must be made credible that essentially all of the claimed matter solves the given problem. With the present scope of the claims this is not the case. The "heteroaryl" expressions in the claims are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description. Accordingly, the said expressions should be restricted in this respect to the particular meanings specified in the description e.g. page 3 (Article 6 PCT). It should be borne in mind that only those compounds which are suitable for solving the problem underlying the present application can be claimed.

- 4). The precise scope of claims 15 and 16 is unclear. The diseases to be treated are not defined directly, but are instead defined in terms of diseases which can be treated by certain antagonists. This is a definition of a disease by means of a result to be achieved and therefore lacks clarity. The said claims should instead list the specific diseases which can be treated as is for instance done on pages 7 and 8.
- 5). Claim 9 is an unallowable reference to the description (Rule 6.2 PCT). The claims should be clear in their own right. It would be appropriate to list examples 1-73 in the said claim.
- 6). Claim 6 appears to lack a true counterpart in the description (Article 6 PCT).
- 7). The first paragraph on page 11 should be deleted.
- 8). The citation on page 1, line 13 of WO98/50538 is a mistake. It appears likely that WO98/50358 was meant.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09442

- 9). The Applicant has not cited the prior art documents (E) and (F) (Rule 5.1 (a) (ii) PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ADS/P32422	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/09442	International filing date (day/month/year) 21/09/2000	(Earliest) Priority Date (day/month/year) 25/09/1999
Applicant SMITHKLINE BEECHAM P.L.C. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



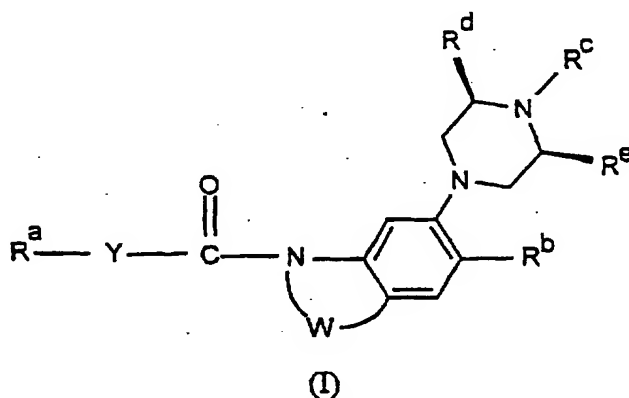
because this figure better characterizes the invention.



None of the figures.

B x III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

Piperazine derivatives of formula (I) processes for their preparation, pharmaceutical compositions containing them and to their use in therapy as 5-HT_{1B} antagonists



W, Y, R^a - R^e are so defined in the application.

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/09442

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/10 C07D413/10 C07D209/08 C07D403/10 C07D401/14
C07D401/12 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50358 A (GASTER LARAMIE MARY ; RAMI HARSHAD KANTILAL (GB); WYMAN PAUL ADRIAN) 12 November 1998 (1998-11-12) claim 1	1-16
X	WO 98 47885 A (GASTER LARAMIE MARY ; WYMAN PAUL ADRIAN (GB); SMITHKLINE BEECHAM PL) 29 October 1998 (1998-10-29) cited in the application claim 1	1-16
X	WO 95 06637 A (SMITHKLINE BEECHAM PLC ; GASTER LARAMIE MARY (GB); DUCKWORTH DAVID) 9 March 1995 (1995-03-09) cited in the application claim 1	1-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

12 December 2000

Date of mailing of the international search report

25/01/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/09442

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 27058 A (WYMAN PAUL ADRIAN ;BROMIDGE STEVEN MARK (GB); KING FRANCIS DAVID () 25 June 1998 (1998-06-25) cited in the application claim 1 ---	1-16
A	WO 99 29666 A (GASTER LARAMIE MARY ;WYMAN PAUL ADRIAN (GB); SMITHKLINE BEECHAM PL) 17 June 1999 (1999-06-17) cited in the application claim 1 ---	1-16
A	EP 0 533 268 A (GLAXO GROUP LTD) 24 March 1993 (1993-03-24) cited in the application claim 1 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 00/09442

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9850358 A	12-11-1998	AU 7431098 A CN 1260781 T EP 0975593 A NO 995065 A PL 336317 A	27-11-1998 19-07-2000 02-02-2000 15-10-1999 19-06-2000
WO 9847885 A	29-10-1998	EP 0975614 A	02-02-2000
WO 9506637 A	09-03-1995	DE 69417427 D DE 69417427 T EP 0716650 A JP 9502177 T US 5696122 A	29-04-1999 25-11-1999 19-06-1996 04-03-1997 09-12-1997
WO 9827058 A	25-06-1998	EP 0946551 A	06-10-1999
WO 9929666 A	17-06-1999	NONE	
EP 0533268 A	24-03-1993	AP 303 A AU 656021 B AU 2453092 A CA 2078505 A CN 1071919 A CZ 9202854 A FI 924160 A HU 65608 A IL 103198 A JP 6116251 A MX 9205280 A NO 923618 A NZ 244373 A PL 295960 A RU 2077535 C US 5510350 A US 5340810 A ZA 9207108 A CN 1076195 A	28-01-1994 19-01-1995 25-03-1993 19-03-1993 12-05-1993 14-04-1993 19-03-1993 28-07-1994 18-06-1996 26-04-1994 01-03-1993 19-03-1993 28-03-1995 06-09-1993 20-04-1997 23-04-1996 23-08-1994 08-09-1993 15-09-1993